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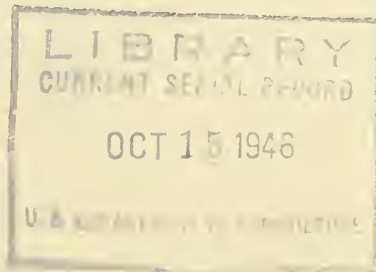
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RUTIN: TREATMENT FOR ARTERIAL HYPERTENSION
CHARACTERIZED BY INCREASED
CAPILLARY FRAGILITY

The contents of this brochure are reproductions of charts which were exhibited at the Scientific Assembly of the American Medical Association, San Francisco Session July 1--5, 1946



This exhibit was awarded a Certificate of
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PETECHIAL INDEX*
AFTER GOTHLIN TECHNIQUE

1. A circular area, 6 cm. in diameter, is marked off in each antecubital space.
2. First stage: Inflate a blood pressure cuff about each upper arm to 35 mm. of mercury for 15 minutes. Thereafter, count the petechiae.
3. Second stage: After one hour, repeat, using 50 mm. cuff pressure.

C A L C U L A T I O N

Petechiae 1st stage x 2

+ petechiae 2nd stage = P. I.*

Normal = 8 (or less)

Increased = 13+

Borderline, probably increased, 9 - 12.

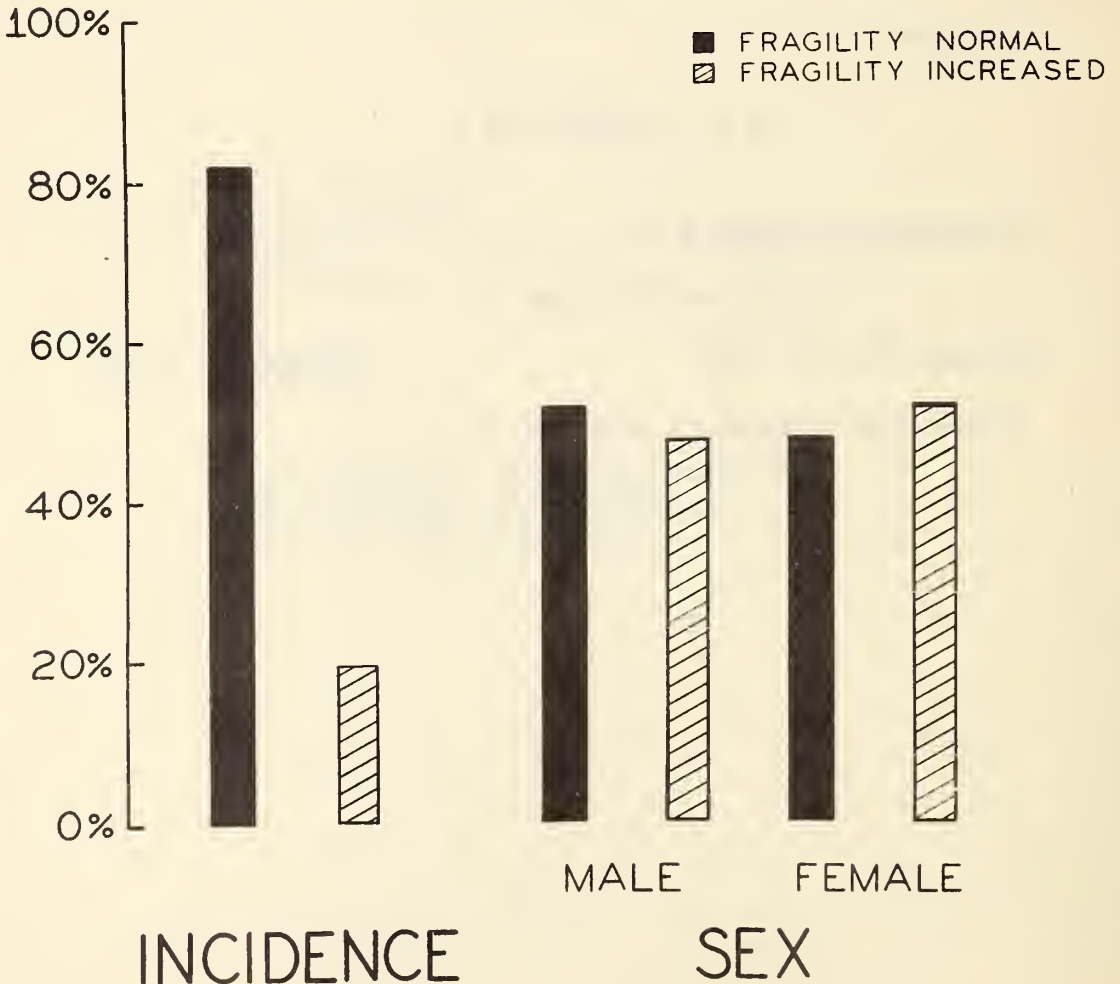
CLINICAL MATERIAL

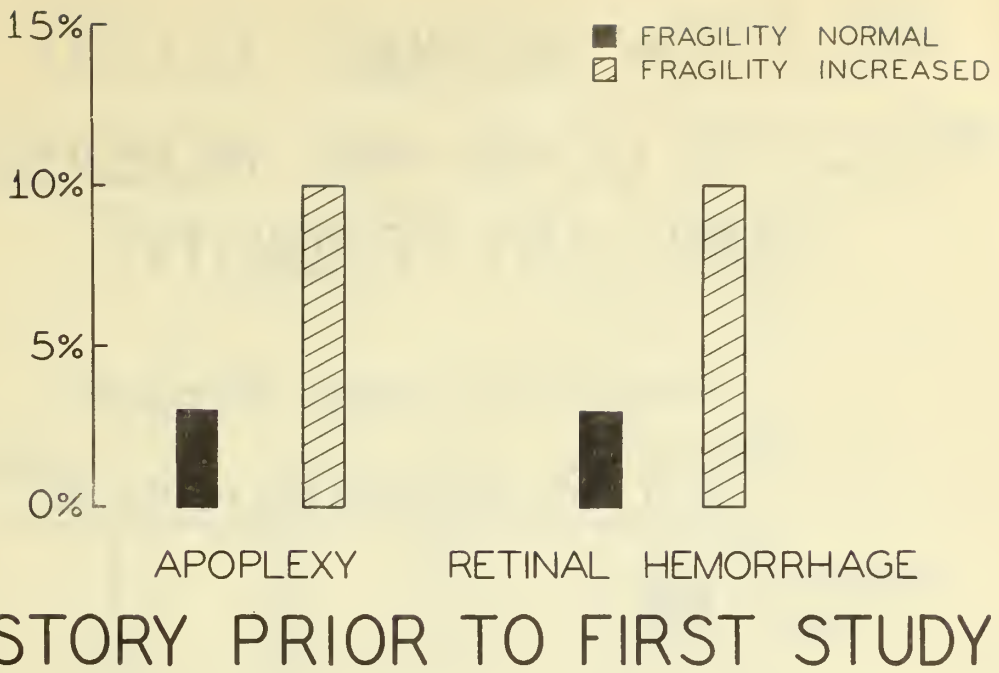
NUMBER OF CONSECUTIVELY STUDIED
WHITE SKINNED HYPERTENSIVES - - - - 1600

NUMBER WITH INCREASED CAPILLARY
FRAGILITY - - - - - 306




















NUMBER ADEQUATELY FOLLOWED - - - 189

AVERAGE FOLLOW UP IS 11 MONTHS,
RANGE 3 TO 36 MONTHS.





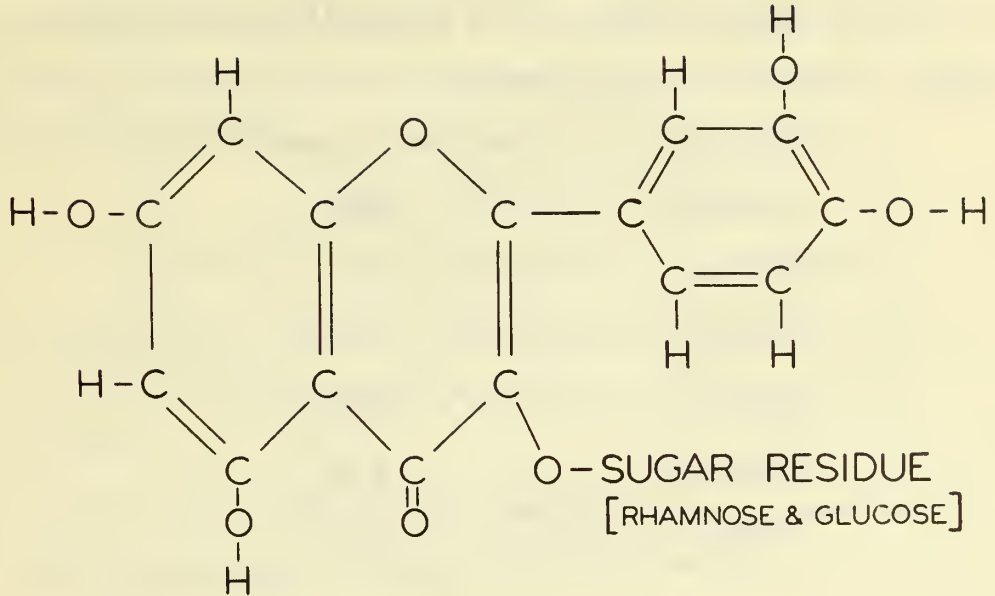
RELATION BETWEEN BLOOD PRESSURE LEVEL AND INCREASED CAPILLARY FRAGILITY*

		DIASTOLIC BLOOD PRESSURE				
		BELOW 100	100-119	120-139	140-159	AND UP 160
SYSTOLIC BLOOD PRESSURE	BELOW 140					
	140-159					
	160-179					
	180-199					
	200-219					
	220 AND UP					

*ALL SUBJECTS CHARTED SHOWED INCREASED CAPILLARY FRAGILITY.

RUTIN

[C₂₇H₃₀O₁₆]



RUTIN IS A NON-TOXIC FLAVONOL GLUCOSIDE THAT OCCURS IN THE BUCK-WHEAT PLANT, PANSY AND FORSYTHIA FLOWERS, ELDER, EUCALYPTUS, TOBACCO AND THIRTY OTHER PLANTS. IT WAS FIRST PREPARED FROM TOBACCO. THE PRESENT COMMERCIAL SOURCE IS BUCK-WHEAT LEAVES AND FLOWERS.

RUTIN DOSAGE

Initial dose is 20 mgm. 3 times daily, by mouth, increased until Gothlin test becomes normal. Gothlin test is repeated every 6 weeks so long as previous test is abnormal; thereafter, every 3 months.

Daily dosage	Per cent of cases
60 mgm - - - - -	72%
80 mgm - - - - -	15%
100 mgm - - - - -	3.5%
120 mgm - - - - -	7.0%
150 mgm - - - - -	2.0%
180 mgm - - - - -	0.5%

RESULT OF RUTIN THERAPY

I. ON CAPILLARY FRAGILITY

	Per cent of cases
Gothlin Test became normal - - - - -	75%
Gothlin Test became borderline - - - - -	15%
Gothlin Test became normal but relapsed - - -	4%
Gothlin Test remained positive - - - - -	6%

EFFECT OF RUTIN THERAPY
II. ON CLINICAL SYMPTOMS

	Per cent of cases
No symptoms initially - - - - -	47%
Symptoms definitely improved - - - - -	30%
Symptoms probably improved - - - - -	13%
Symptoms unchanged - - - - -	10%

EFFECT OF RUTIN THERAPY

III. ON THE INCIDENCE OF APOPLEXY

- 1 Patient, while taking rutin and with a normal Gothlin Index, developed apoplexy and died. He was also in uremia.
- 1 Patient whose Gothlin Test remained increased consistently, suffered an attack while taking rutin.
- 1 Patient failed to report on schedule but died of apoplexy 4 months after a normal Gothlin Test, while allegedly taking rutin.
- 4 Patients suffered apoplexy 1 to 4 months after discontinuing rutin.

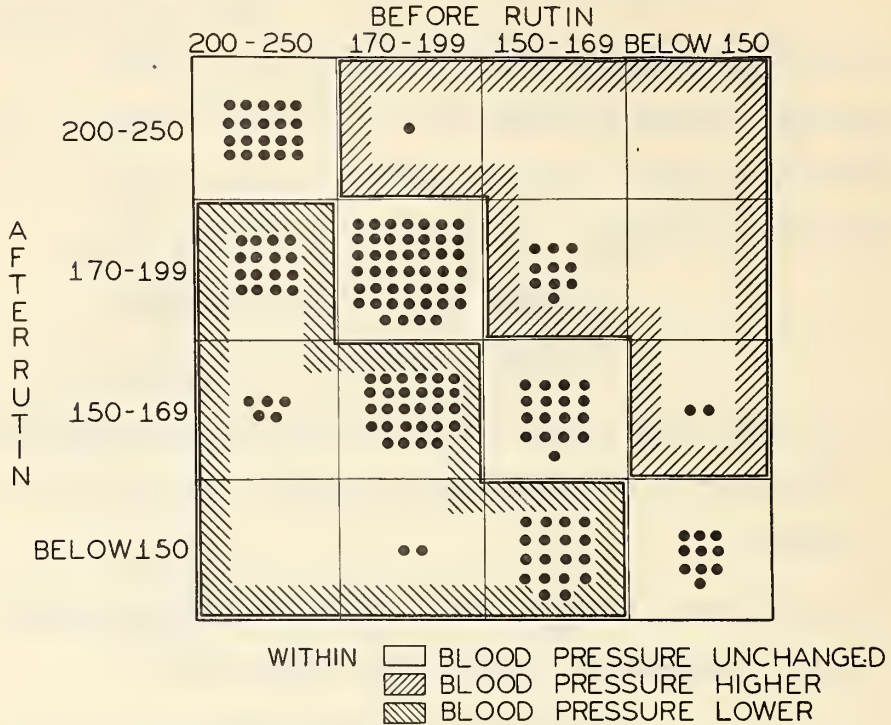
EFFECT OF RUTIN THERAPY

IV. ON THE INCIDENCE OF RETINAL HEMORRHAGE

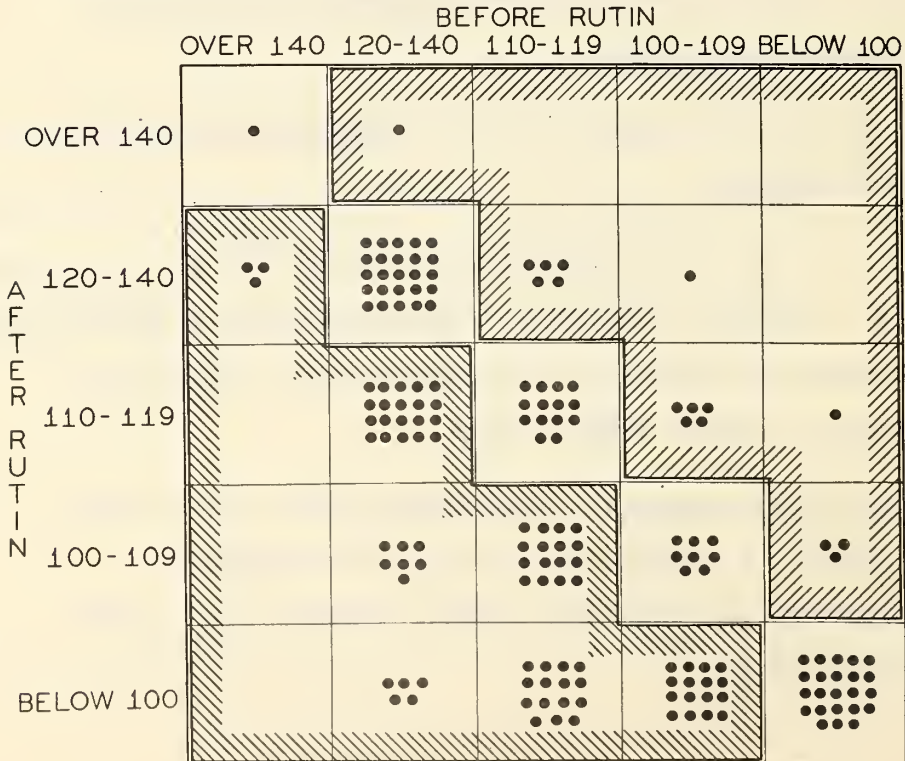
- 2 Patients had subsequent hemorrhages while taking rutin and with a normal Gothlin Index.
- 4 patients had subsequent hemorrhages while taking rutin but while the Gothlin Index remained increased.
- 1 Patient had a hemorrhage about 2 months after discontinuing therapy.

EFFECT OF RUTIN

V. ON SYSTOLIC BLOOD PRESSURE



VI. ON DIASTOLIC BLOOD PRESSURE



RELATION TO THIOCYANATE THERAPY

The following items are considered suggestive but not conclusive;

1. During the past 2 years capillary fragility, which was initially normal, became increased in 6 patients following the institution of thiocyanate. This comprises only a small per cent of the persons given thiocyanate.
2. In 7 instances the following occurred; A patient with increased fragility was given rutin, and the fragility became normal. After a period of stabilization thiocyanate was begun and the fragility again became increased. The dose of rutin was increased, the thiocyanate continued, and fragility again became normal.
3. In past years we have noted that the institution of thiocyanate therapy is rarely followed by apoplexy or retinal hemorrhage.
4. Further direct study along this line appears unjustified, but it seems reasonable to believe that, in a small number of cases and perhaps as an idiosyncrasy, thiocyanate may tend to increase capillary fragility and predispose to apoplexy or retinal hemorrhage. We do not give thiocyanate to patients with increased capillary fragility, but wait until fragility has become normal following treatment of at least 3 months. Thereafter, Gothlin test is repeated every 6 weeks to 3 months, and a return of positive test usually requires cessation of thiocyanate therapy, or an increase in rutin dosage.

CONCLUSIONS

1. Increased capillary fragility, measured by the method of Gothlin, occurs in about 18% of hypertensive subjects.
2. Hemorrhagic complications, as apoplexy and retinal hemorrhage, are more common in persons with increased fragility. Considering the small size of the group with increased fragility, however, it is to be noted that the actual figure for persons with apoplexy is divided about equally between the two groups.
3. Increased capillary fragility can usually be reduced to normal by rutin, and patients so treated appear to be protected against apoplexy and retinal hemorrhage so as to become comparable with the originally normal group. Unfortunately, separation of an untreated control group was considered unjustified.
4. Successful rutin therapy may lower blood pressure and relieve symptoms, but this effect is variable.
5. In persons with increased fragility, rutin therapy may be a preliminary to and continued along with, thiocyanate therapy, thus securing a further lowering of blood pressure.

ADDENDA CONCERNING
INCREASED CUTANEOUS LYMPHATIC FLOW

1. During the past year, it has become apparent that increased capillary fragility and increased cutaneous lymphatic flow bear a relation to each other and, probably to the same underlying pathologic process. These observations are preliminary.
2. Increased cutaneous lymphatic flow indicates passage of fluid through the capillary wall, which may be due to either increased capillary pressure or increased capillary permeability.
3. Increased capillary pressure is apt to be associated with either pituitary or kidney disease.
4. It is probable that increased capillary permeability is often associated with increased capillary fragility. In the present series, 36% of the subjects with increased fragility showed increased cutaneous lymphatic flow.
5. When increased capillary fragility and increased cutaneous lymphatic flow are associated, both become normal after rutin therapy.

6. Increased cutaneous lymphatic flow not associated with increased fragility, pituitary or kidney disease, also usually becomes normal after rutin therapy (12 out of 17 cases).
7. Thiocyanate is ineffective in lowering blood pressure in persons with increased cutaneous lymphatic flow, and its use may be followed by actual edema. It is effective after the condition has been corrected by rutin.
8. In 105 persons with increased capillary fragility and increased cutaneous lymphatic flow, apoplexy occurred 13 times and retinal hemorrhage 9 times. In 42 persons with increased cutaneous lymphatic flow and normal capillary fragility, apoplexy and retinal hemorrhage occurred, each, 5 times.
9. The above patients with increased cutaneous lymphatic flow only have been on rutin therapy for a short period, up to 10 months. No further apoplexy has occurred, but one has had another retinal hemorrhage, coming on 3 weeks after cutaneous lymphatic flow had again become increased.

TECHNIQUE FOR MEASURING CUTANEOUS
LYMPHATIC FLOW

1. The blue colloidal dye, patent blue, is used, purified according to the method of McMaster.
2. One injects intracutaneously 0.04 c.c. of the dye in the antecubital space and follows the spread of streamers for 15 minutes. Spread during the first minute is due to the force of the injection. From the first to the 15th minute, the spread should be no more than $\frac{3}{4}$ ths of an inch. A greater spread indicates an increased flow.
3. The color disappears, always within 2 days, often in 18 hours. In some 5000 tests no reaction has occurred and no permanent discoloration resulted. Rarely, a transient redness is seen about the area of injection, lasting one hour.

RELATION BETWEEN RUTIN AND CRUDE HESPERIDIN INCREASED CAPILLARY FRAGILITY IN HYPERTENSION: INCIDENCE, COMPLICATIONS, AND TREATMENT

J. Q. Griffith, Jr.,* M. D., and M. A. Lindauer, M. D.
Philadelphia, Pa.

In 1940, Paterson¹ stated: "capillary rupture with intimal hemorrhage in relation to the precipitation of coronary thrombi has been described...." by Paterson,² Wartman,³ and Winternitz and his coworkers.⁴ He goes on to state: "capillary rupture with intimal hemorrhage is intimately concerned with the mechanism of cerebral arterial thrombosis and possibly, in certain cases, with the causation of cerebral arteriospasm and rupture. It is suggested that the factors responsible for the rupture of intimal capillaries in the cerebral arteries are high intracapillary pressure from hypertension, progressive atheromatous degeneration of the supporting tissue and increased capillary fragility from a variety of causes."

It seemed possible, therefore, that an abnormal condition of the capillaries might be a factor in the production of certain of the vascular accidents which sometimes occur in cases of hypertension. We were especially interested in the relation of such complications to thiocyanate therapy, for we had noted cutaneous ecchymoses rather commonly, retinal hemorrhages less commonly, and apoplexy and coronary occlusion very rarely after the initiation of such therapy. The more serious complications were rare enough to suggest that they were merely coincidental, yet were regarded as alarming nevertheless.

Method and Material

For a period of eighteen months all persons with hypertension who were routinely studied in our laboratory had, in addition, a measurement of capillary fragility by the Petechial Index of Göthlin,⁵ with certain minor modifications.

TECHNIQUE OF THE TEST.--(1) Mark off a circular area, 6 cm. in diameter, in each antecubital area. Mark off all blemishes and marks in this area that might later be confused with petechiae. (2) Place a standard blood pressure cuff about each arm, and maintain in each a pressure of 35 mm. of mercury for fifteen minutes. Lower the pressure, and count and mark all petechiae within the two circular areas, using a good light and a magnifying lens of 5 D or its equivalent. (3) One hour or more later, repeat, using a cuff pressure of 50 mm. of mercury.

The Petechial Index is calculated as follows: To the number of petechiae occurring at 35 mm. of mercury multiplied by 2, add the additional number occurring at 50 millimeters. Based upon the Petechial Index, capillary fragility is considered to be: (a) normal, if the Index is 8 or less, (b) increased (abnormal) if the Index is 13 or more, and (c) borderline, but probably abnormal, if the Index is 9 to 12.

In order to save time, the second stage can be omitted under the following conditions: (1) The number of petechiae after the first stage is 2 or less. Such persons may be considered normal. Usually, but not invariably, the person is normal who has 3 petechiae after the first stage. (2) If 6 or more petechiae appear after the first stage, the subject may be considered abnormal. (3) The test is a repetition, and may be compared with the corresponding first stage of an earlier test. Repetition in less than three weeks, however, is unreliable in any case.

The second stage should always be done if the fragility is being tested in a subject for the first time and there are 4 or 5 petechiae after the first stage. It should also be done in most cases when the number after the first stage is 3.

The patients, 265 in all, had history and physical examination by various members of our hospital staff and referring physicians. Special attention was paid to the following: (1) history suggesting apoplexy, (2) history of spontaneous cutaneous ecchymoses, (3) presence of retinal hemorrhages, as ascertained by ophthalmoscopic examination, and (4) simultaneous medication with thiocyanate.

Ophthalmoscopic examination was carried out by physicians with varying degrees of skill, so that the occurrence of retinal hemorrhages as a positive sign may be accepted, whereas their absence did not necessarily entirely exclude them.

The period of study was never less than six months nor more than twenty months.

Thirty-three patients with increased fragility were treated with Hesperidin* by mouth in a dose of 250 to 500 mg. three times a day, and nine more were given Hesperidin Methyl Chalcone* by mouth in a dose of 10 mg. three times a day. In addition, fourteen such patients were treated with Rutin, the result of which has already been reported.⁶

Results

1. **INCIDENCE OF INCREASED CAPILLARY FRAGILITY:** As shown in Fig. 1, capillary fragility was found to be normal in 218 of the series, or 82 per cent (approximately). It was definitely increased in 44 subjects, whereas, in three, it was borderline, making a total of 47 persons, or 18 per cent (approximately), whose capillary fragility was, at least, not normal. Judging from the occurrence of complications, it appears that the borderline group should be classed as definitely abnormal.

* Supplied by Abbott Laboratories, North Chicago, Ill.

2. **RELATION OF CAPILLARY FRAGILITY TO SEX AND AGE:** As shown in Fig. 1, there was no significant relationship between capillary fragility and either sex or age.

3. **RELATION OF CAPILLARY FRAGILITY TO BLOOD PRESSURE LEVEL:** Fig. 2 shows the systolic and diastolic blood pressure of 54 patients with increased capillary fragility. There was obviously no relationship between the occurrence of increased capillary fragility and blood pressure level. This series of 54 patients was obtained by adding to the original series of 47, seven subjects from an earlier group who were called back for study because they had developed one or more of the "complications" of increased fragility.

4. **RELATION OF CAPILLARY FRAGILITY TO THE OCCURRENCE OF APOPLEXY:** A history of apoplexy, followed by paralysis, was obtained in four cases, or 2 percent (approximately) of the patients whose capillary fragility was normal. Four more subjects in this group gave an atypical history, namely, that a diagnosis of apoplexy had at one time been made (usually severe headache was described as a "slight stroke"), but there never was any paralysis, nor were there any neurological sequelae at the time the patient was studied. If these were included, it would raise the incidence of apoplexy in the group with normal fragility to 4 per cent. On the other hand, seven of the patients with increased fragility gave a definite history of apoplexy followed by paralysis, and five more had strokes during the period of observation, making a total incidence in the group of twelve, or 25 per cent (approximately). It would appear, therefore, that apoplexy occurred with greater frequency in persons with hypertension associated with increased fragility than in those with normal capillary fragility.

5. **RELATION OF CAPILLARY FRAGILITY TO THE OCCURRENCE OF RETINAL HEMORRHAGES:** Retinal hemorrhages were recognized in five persons with normal capillary fragility, or 2 per cent (approximately), and in ten persons, or 21 per cent (approximately), whose capillary fragility was increased. It seems likely, therefore, that retinal hemorrhages occur more commonly in those persons with hypertension whose capillary fragility is increased.

6. **RELATION OF CAPILLARY FRAGILITY TO THIOCYANATE MEDICATION:** Ten persons were studied who were attending our dispensary and receiving thiocyanate prior to the beginning of this investigation. These persons were chosen because all of them showed either cutaneous ecchymoses (nine cases) or retinal hemorrhages (one case) beginning soon after the onset of thiocyanate medication. All ten persons showed an increase in capillary fragility. Three other patients with increased capillary fragility were given thiocyanate without other treatment. One patient developed cutaneous ecchymoses, one developed retinal hemorrhages, and the third died of a stroke. We have not felt justified in continuing this phase of the study, but have made it a rule never to give thiocyanate to a patient with increased capillary fragility until, or unless, that fragility has become normal as the result of treatment. Thiocyanate therapy has been used in twelve such cases without incident.

7. **RELATION OF CAPILLARY FRAGILITY TO MORTALITY:** During the twenty months' period of study there were three deaths in the group with normal

fragility, or 1 per cent (approximately), and five deaths, or 10 per cent (approximately), in the group with increased fragility. It seems probable that the mortality is greater among persons with hypertension and increased capillary fragility than among those with hypertension and normal fragility.

8. **EFFECT OF TREATMENT:** Hesperidin was given to 33 persons with increased capillary fragility, only 23 of whom were adequately followed. In 20 of these, capillary fragility, as measured by Göthlin's test, became normal within one or two months after starting treatment, and remained so thereafter except in two instances, in which the patient discontinued treatment without permission, when the test became abnormal, to become normal again when treatment was resumed. In three subjects the capillary fragility was not affected by treatment and remained abnormal; two of these developed apoplexy and died. One of the 20 patients whose fragility returned to normal after therapy also died of apoplexy. This patient had a high degree of papilledema when first seen.

Hesperidin methyl chalcone was given to nine persons with increased capillary fragility. In seven of these the fragility became normal, while two were unaffected. This group has been followed only six to nine months, and no complications have occurred in any of the nine subjects.

We have not felt justified in discontinuing medication at intervals to secure adequate controls for its effectiveness. Also, one cannot say with the evidence at hand that reversion of Göthlin's test to normal indicates that the subject is less likely to suffer one of the hemorrhagic complications of hypertension, but it seems likely that such is the case.

Summary

1. Capillary fragility was increased in about 18 per cent of 265 cases of hypertension. This incidence was not related to sex, age, or degree of hypertension.

2. Persons with increased capillary fragility are especially predisposed to apoplexy, retinal hemorrhage, and death.

3. Thiocyanate tends to make worse a previously abnormal fragility, or perhaps in certain cases may even change fragility from normal to increased. When this occurs, thiocyanate may be a factor in the causation of apoplexy and other hemorrhagic phenomena.

4. Hesperidin and hesperidin methyl chalcone restored fragility to normal in about 84 per cent of cases of increased capillary fragility. It is hoped, but not yet proved, that this may also lessen the frequency of the complications of increased capillary fragility.

5. It is probable that thiocyanate should not be given to persons with increased capillary fragility, unless or until that fragility has become normal as the result of therapy. After this has been done, thiocyanate apparently can be given with impunity.

CAPILLARY FRAGILITY

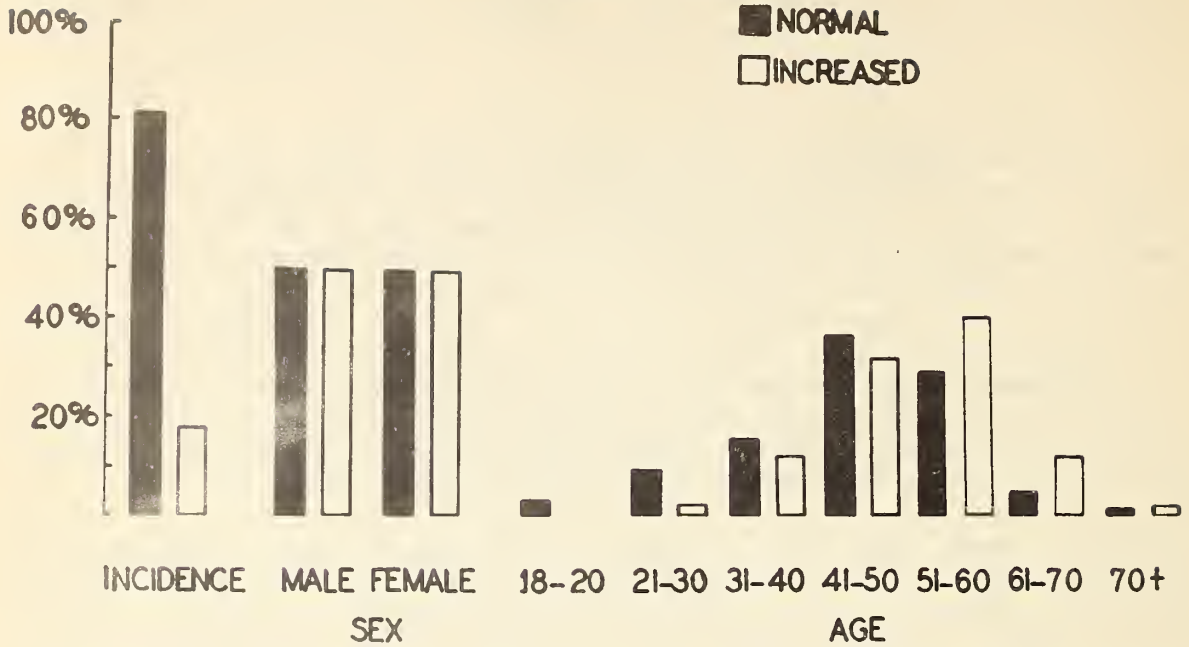


Fig. 1.—Chart comparing the incidence of normal and increased capillary fragility in the general hypertensive group (on the left) and in groups selected on the basis of sex and age. The figures for the two columns on the left are expressed as percentage of the entire group of 265 cases. The percentage figures for sex and age, however, refer only to the total group with normal fragility (filled-in rectangle) or increased fragility (open rectangle). The age is expressed in years.

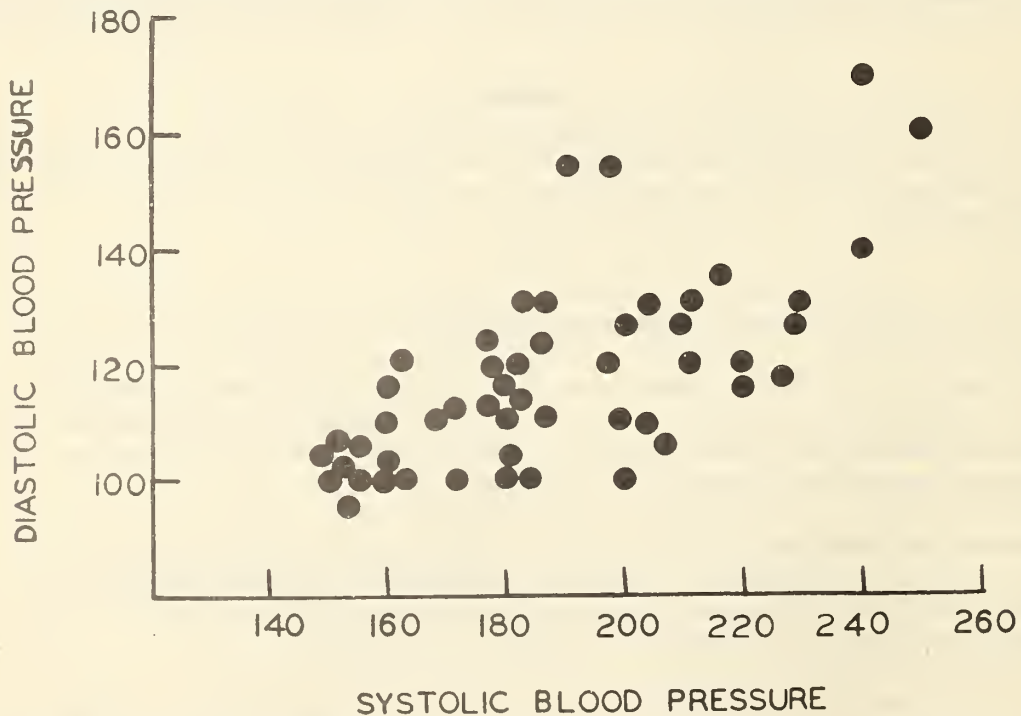


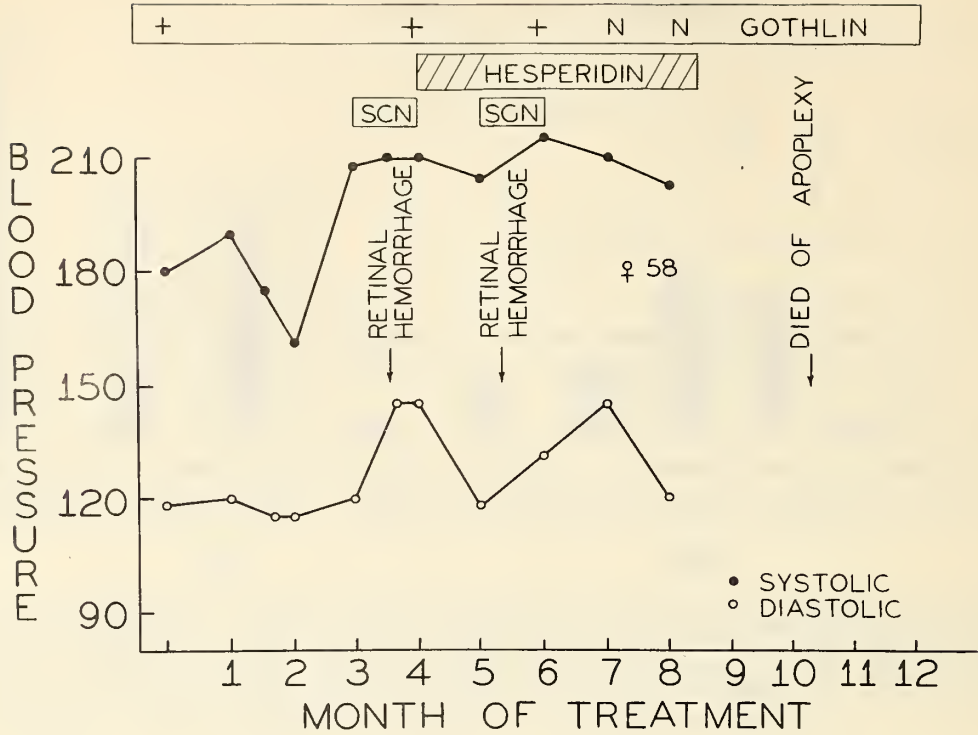
Fig. 2.—Chart showing the systolic and diastolic blood pressure of 54 persons with increased capillary fragility. Each dot represents one subject.

References

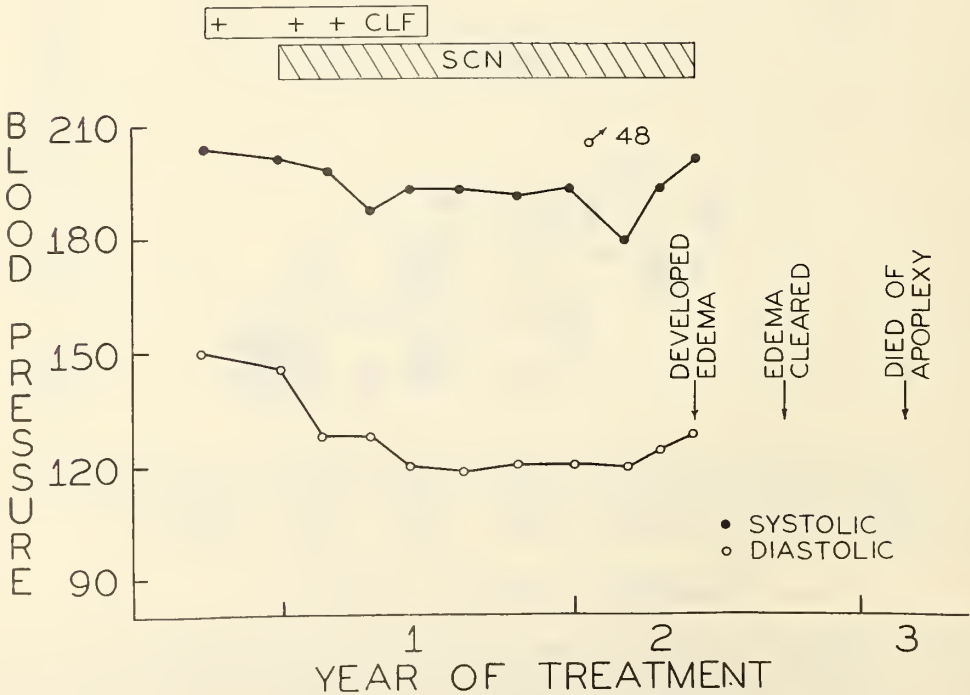
- 1 Paterson, J. C.: Capillary Rupture With Intimal Hemorrhage in Causation of Cerebral Vascular Lesions, Arch. Path. 29: 345, 1940
- 2 Paterson, J. C.: Vascularization and Hemorrhage of Intima of Arteriosclerotic Coronary Arteries, Arch. Path. 22: 313, 1936.
- 3 Wartman, W. B.: Occlusion of Coronary Arteries by Hemorrhage Into Their Walls, Am Heart J. 15: 459, 1938
- 4 Winternitz, M. C., Thomas, R. M., and LeCompte, P. M.: The Biology of Arteriosclerosis, Springfield, 1938, Charles C. Thomas
- 5 Ahlborg, N. G., and Brante, G.: Parallel Investigations Into Ascorbic Acid (Vitamin C) Content in Blood Plasma and Into Strength of Cutaneous Capillaries in Healthy Children, Acta med. Scandinav. 104: 527, 1940
- 6 Griffith, J. Q., Jr., Couch, J. F., and Lindauer, M. A.: Effect of Rutin on Increased Capillary Fragility, Proc. Soc. Exper. Biol. & Med. 55; 228, 1944

Crude Hesperidin in most instances has a therapeutic effect identical with rutin. An occasional supply of crude Hesperidin, however, is inactive. Rutin has the advantage of being a chemically pure substance and hence of uniform activity, and is effective in much smaller doses than crude Hesperidin.

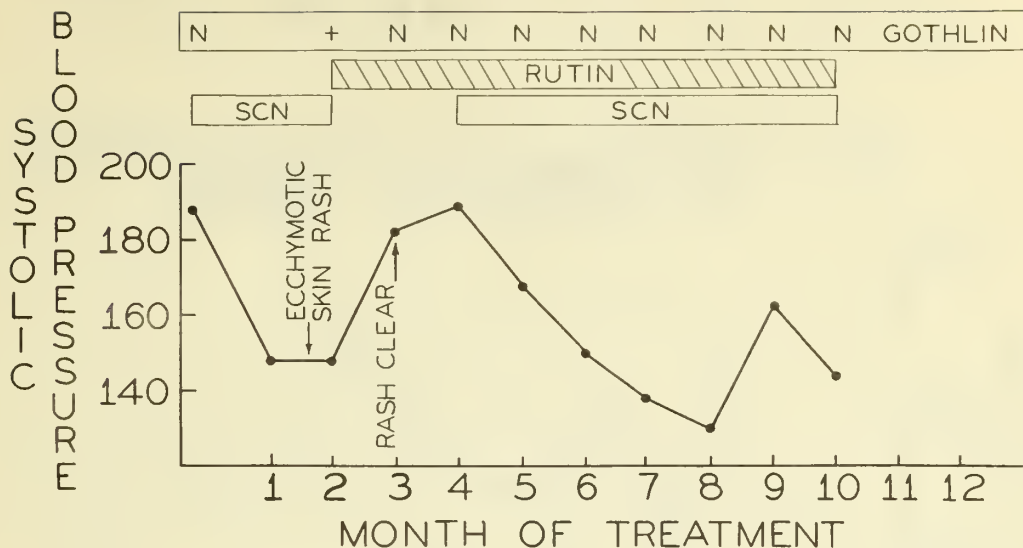
CASE 1



CASE 2

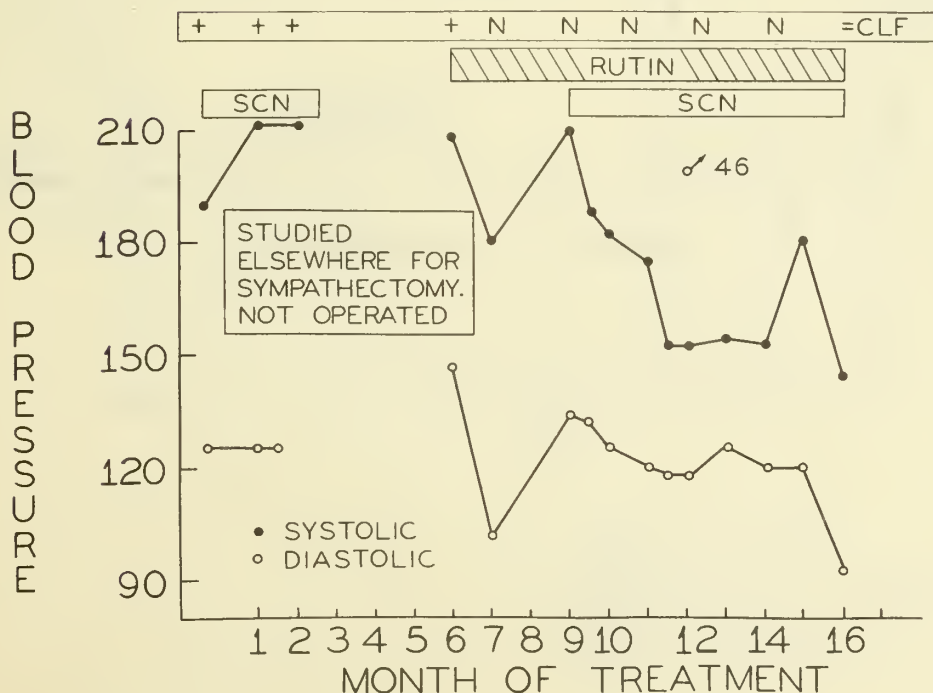


CASE 3

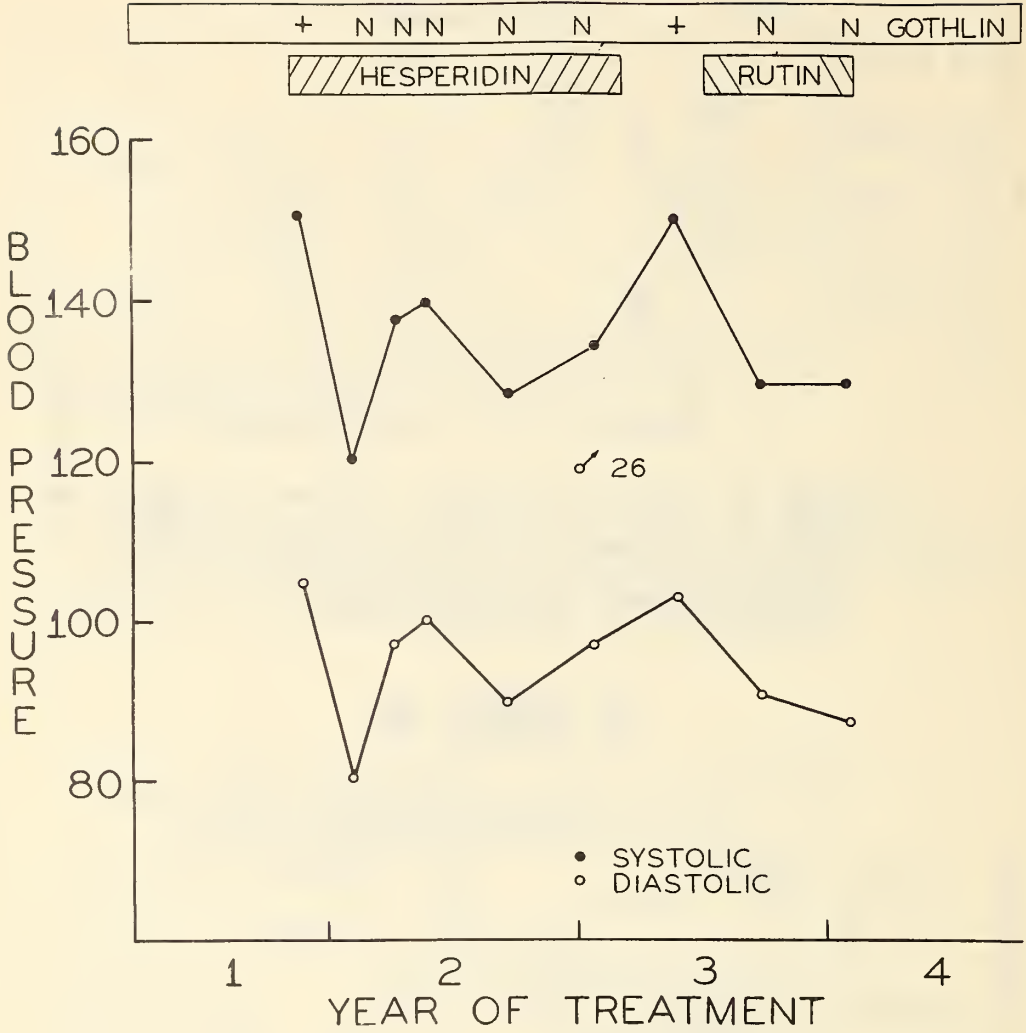


♀ 55 WITH THIOCYANATE THERAPY, SATISFACTORY DROP IN PRESSURE OCCURS, BUT CAPILLARY FRAGILITY BECOMES INCREASED AND ECCHYMOTIC SKIN RASH APPEARS. AFTER INTERVAL OF RUTIN THERAPY ALONE, RASH DISAPPEARS AND THEN THIOCYANATE IS RESUMED.

CASE 4

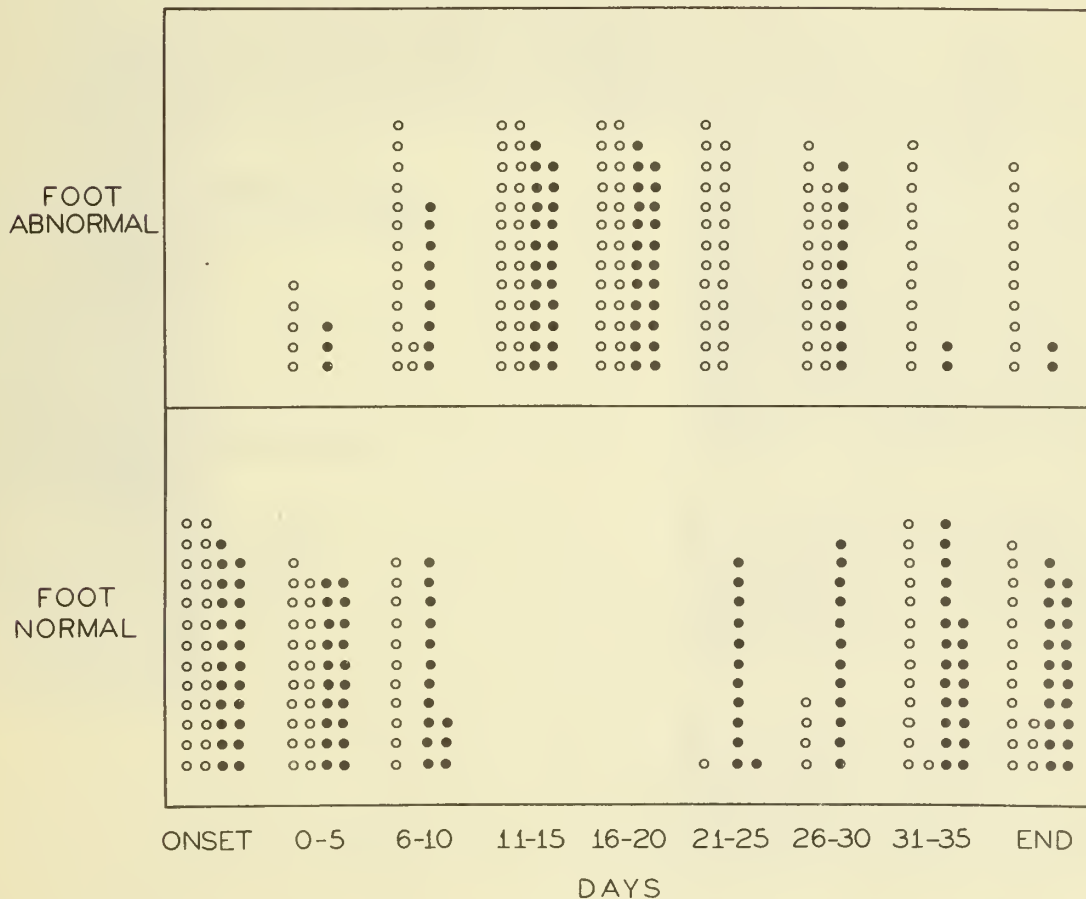


CASE 5



EFFECT OF RUTIN ON RECOVERY FROM IRRADIATION IN RATS

ALL RATS GIVEN 2385 R TO ONE FOOT, IN ONE TREATMENT.



- NORMAL CONTROL
- GIVEN RUTIN BY PELLET IMPLANTATION, 20 MGM. EVERY THIRD DAY

